REMARKS

I. Status of the Claims

Claims 1-9 and 11 are currently pending. Upon entry of this amendment, these claims are canceled without prejudice or disclaimer and new claims 19-30 introduced. The new claims are supported throughout the specification including, for example, at the following sections:

Claims 19, 20 and 29: page 24, line 20 to page 25, line 8.

Claims 21-23: page 25, lines 26-33.

Claims 24-28 and 30: page 26, line 15 to page 27, line 30

II. Priority

The specification has been amended to include the priority claim as the first paragraph of the specification. The claim to priority to the 09/138,958 application was made in the transmittal letter, including incorporation of the application by reference. Hence, this amendment adds no new matter.

III. Double Patenting

Claims 2-5 and 11 stand rejected based upon the same invention type of double patenting. As these claims have been canceled, this rejection is rendered moot.

Claims 1 and 6-9 stand rejected on the basis of obviousness type double patenting. Cancellation of these claims has rendered this rejection moot.

With respect to the current claims, Applicants are enclosing a terminal disclaimer herewith.

IV. Rejection under 35 U.S.C. 112, second paragraph

The rejection of claims 6 and 7 as allegedly being indefinite is rendered moot in view of the cancellation of these claims.

V. Rejection under 35 U.S.C. 102 and 103

Claims 1, 6, 8, 9 and 11 stand rejected as allegedly being anticipated or rendered obvious by PCT publication WO 95/11995 to Chee et al. ("Chee"). The cancellation of these claim renders these grounds for rejection moot.

New claims 19, 20 and 29 describe arrays and methods of using such arrays that have at least three components: (i-ii) first and second component probes that are respectively complementary to nonoverlapping segments of a mRNA molecule and (iii) a mismatch probe in which the mismatch probe has the same sequence of as one of the first and second component probes, or a pool of mismatch probes in which the probes have the same sequence as the first and second component probes except for a single base pair mismatch.

While Chee discusses certain arrays and methods using groups of pools to conduct various types of nucleic acid analyses, Chee does not teach or suggest arrays or the use of arrays that include the three probe components set forth in these claims.

New claims 21-23 are directed to arrays that comprise plurality of sets of nucleic acid probes. Each set comprises a plurality of pools; these pools in turn comprise a first probe and a second probe. First probes within any given set have the same sequence; however, first probes in different sets have different sequences (e.g., first probes in different sets are complementary to different markers – see claim 22). The second probe differs in sequence from the first probe within a pool. In certain arrays, (e.g., as described in claim 23), within any given set of probes, the second probes are the same length and collectively represent all possible sequences having that length.

Again, while Chee discusses various types of arrays, Chee does not teach or suggest arrays having the particular grouping of probes as described in claims 21-23.

New claims 24-28 and 30 describe arrays in which probe mixtures are bound to different regions of a support. Each of these mixtures comprises an interrogation probe and a partner probe. The interrogation probes within any given mixture are complementary to a first segment of a reference nucleic acid that contains an interrogation position and have the same sequence except at the interrogation position, each interrogation probe within a mixture having one of the four nucleotide bases. The partner probe is complementary to a second segment of the

reference nucleic acid that does not overlap the first segment. Different probe mixtures have different interrogation probes.

While Chee discusses certain types of arrays that contain sets of probes that differ only at an interrogation position, Chee does not teach or suggest the arrays or methods of using arrays in which interrogation probes are utilized in conjunction with a partner probe that is complementary to a segment that does not overlap the segment to which the interrogation probes are complementary.

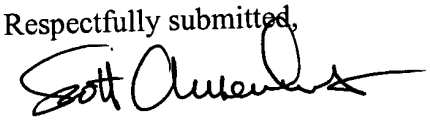
Thus, for the foregoing reasons, the currently pending claims are believed to be allowable over the cited art.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 303-571-4000.

Respectfully submitted,



Scott L. Ausenhus
Reg. No. 42,271

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: (415) 576-0200
Fax: (415) 576-0300
SLA
DE 7076194 v2

VERSION WITH MARKINGS TO SHOW CHANGES MADE

The paragraph beginning on page 9, line 7 has been amended as follows:

Fig. 4A. Fluorescence images of cooperative vs. non-cooperative hybridization to paired probe arrays. The design of the array is shown in Fig. 3. Unambiguous hybridization to the double perfect match probe pair is shown for four different linked sequence pairs (10g–27c, 10c–27t, 10c–27g, and 10g–27t from top of left hand column). Hybridization images of the corresponding unlinked targets are shown in the adjacent right hand column.

The paragraph beginning on page 9, line 16 has been amended as follows:

Fig. 4[.5]B 50:50 mixtures of (10c–27t and 10g–27c) and (10g–27t and 10c–27c) are shown in the two panels of the left hand column. Although the two experiments have targets that are identical in sequence composition, the pairing is different. This is clearly detected in the experiment, which allows the pairings (linkages) to be determined in each case. The bottom panel in the right hand column shows a hybridization image of (10c, 10g, 27c, and 27t). The sequence composition is identical to the two lower panels of the left hand column. However, in this case the individual targets are unlinked, and hence no cooperative effect is observed.

The paragraph beginning on page 32, line 11 has been amended as follows:

Hybridizations were performed as described in Table 1. Different mixtures of DNA target complementary to Probe 1 and Probe 2 were used to investigate the extra stability of the paired hybridization (Fig. 4A). The fluorescence intensity of the linked targets was always greater than 40x the intensity of their unlinked counterparts. The intensities of the linked targets in the regions where they matched both paired probes were 2-3x the sum of the intensities where they matched just Probe 1 or Probe 2. For the unlinked targets, the intensities in the regions where the targets matched both paired probes was 15-35% less than the sum of the regions where they matched Probe 1 or Probe 2. This 15-35% loss of signal may be due to crowding effects at

the surface, since almost twice as much target is present in the regions where the targets match both probes. The discrimination ratio between the correct calls and single base changes was also markedly better with the linked targets. These results demonstrate the cooperative hybridization of linked target sequences to paired probes. In every case, the linkage or independence of N1 and N2 was clearly distinguished, and the variable bases at N1 and N2 were correctly determined in the physically linked targets.

The paragraph beginning on page 32, line 34 has been amended as follows:

Assignment of linkage in a heterozygous mixture. To determine if hybridization to paired probe arrays could be used to assign linkage directly in complex heterozygotes, two further experiments were conducted. In each case, equimolar mixtures of two linked targets were hybridized to a 9-mer paired probe array. In the first experiment, the mixture consisted of 10c–27t and 10g–27c. In the second experiment, the mixture was of 10g–27t and 10c–27c. Although the two experiments have targets that are identical in sequence composition, the pairing is different. The results are shown in the left-hand bottom two panels of Fig. 4A. In each mixture, it was straightforward to assign linkage. In each case, the linked sequences are clearly discriminated from the other possible arrangements (e.g. c–c, g–t vs. g–c, c–t). Even though the probes in the four array positions c–c, c–t, g–c, g–t are complementary to equimolar amounts of target in the hybridization mixture, there is significantly more signal where the two probes are perfectly complementary to the same target molecule (1.4-7 x intensity). Furthermore, the control hybridization, in which unlinked targets have the same sequence composition as the linked targets, shows lower signal and no evidence of cooperativity. These results show that paired probe arrays can be used to assign linkage in mixtures containing two different multiply polymorphic alleles.

The paragraph beginning on page 37, line 17 has been amended as follows:

PPA = Paired Probe Array

Oligo targets: a, b, c and d are placeholders for different sequences. Actual sequences are given in Fig. 4A.

Buffer A= 6xSSPE, 0.005% Triton X-100

Buffer B= 2.4M Tetraethylammonium Bromide, 10mM Tris pH 7.8, 1mM EDTA, 0.05% Triton X-100

Buffer C= 2.4M Methyltriethylammonium Bromide, 10mM Tris pH 7.8, 1mM EDTA, 0.05% Triton X-100

Label: F = fluorescein, P = phycoerythrin-streptavidin